REMARKS

The August 25, 2004 Office Action has objected to the claims for a number of reasons. First, it was requested that the term "agents" in the preamble of claim 11 be changed to the singular. Applicants have amended Claim 11 to recite ""a method for determining whether an agent will inhibit an angiogenic response". Additionally, Applicants have amended claim 19 to indicate that it depends from claim 11; thus, the objection to claims 16 and 17 is now addressed. Finally, objection to claims 11-17 have been overcome by replacing the term "alpha" with the symbol "α" in claims 12, 15, 16 and 17.

Applicants note that all amendments were made for reasons unrelated to patentability and do not change the scope of the claims, either literally or otherwise. Additionally, no new matter has been introduced into the claims as a result of these amendments

35 USC §112(1) Enablement Rejection

Claims 11-17 have been rejected as allegedly lacking enablement. The Office Action indicates the concern that the specification does not enable any person skilled in the art to which it pertains to make or use the invention in the manner required by the first paragraph of 35 USC §112.

The stated rationale for this rejection is that the person of ordinary skill in the art would not know how to "make and use the alpha subunits recited in the instant claims" because there is allegedly insufficient guidance to direct a person of skill in the art to select an alpha subunit as "essential" for inhibiting VEGF-dependent angiogenesis. See August 25, 2004 Office Action, page 3. Applicants respectfully traverse this rejection.

As an initial matter, Applicants note that claim 17 is drawn to the method of any of claims 11-16 wherein the alpha subunit is the $alpha_V$ subunit. Clearly, there can properly be no claim of ambiguity in the identification of this subunit; thus the Applicants respectfully submit that the rejection does not apply to claim 17.

Additionally, Applicants point out that none of the pending claims contain a limitation wherein the claimed method is used only to screen inhibitors of "VEGF-dependent angiogenesis"; the claims are simply directed to methods of screening inhibitors of "angiogenesis". Thus, this rejection's rational dependence on the selection of alpha subunits essential for inhibiting VEGF-dependent angiogenesis is respectfully

thought to be misplaced.

The Examiner has cited a number of references published after the priority date of this application, among them Bergreson et al., *Biochem. J.* 2003, Ratnikov et al., *J. Biol. Chem.* 277:7377-7385 (2002); and Zhang et al., *Invest. Ophthal. Vis. Sci.* 43:955-962 (2002). As this rejection is not a prior art rejection, the function of these citations in the context of an enablement rejection is not readily apparent.

Whatever the rationale, the Office Action's characterization the present specification and of the cited post-filing art, and thus the conclusions reached in comparing them, is not entirely accurate. For example, on page 3 the Office Action indicates that the specification states that neovascularization of rat corneas in response to alkaline injury (just one example of available assays of angiogenesis) involved angiogenesis along the VEGF/α_VB3 pathway. However, on page 9, lines 14-16, the specification indicates that the pathway is the VEGF/α_VB5 (not the VEGF/α_VB3) pathway. Moreover, the particular experiment which this passage only analyzed integrins α1, α2 , B3 and B5 (as well as CD31 MMP-2 and MT1-MMP); obviously the same experiment, described in detail, can be performed using the other known alpha subunits, such as subunits α_3, α_4, α_5, α_6, α_8, α_9, α_{2b}, α_E and α_V as is clearly described in the specification. Such an assay, may include some experimentation to define those alpha subunits which are involved in angiogenesis. However, the amount of such experimentation cannot properly be considered undue, or indeed anything other than routine, given the guidance of the specification and the level of knowledge (acknowledged by the Examiner on page 4, third paragraph to be high) of those skilled in the art.

Similarly, the Office Action quotes Zhang et al., a post-filing reference, as saying that "in several instances in which VEGF is present both α_VB3 and α_VB3 re expressed". This sentence actually reads ". . . both α_VB3 and α_VB5 are expressed".

Perhaps in part because of conclusions based on these characterizations, the Examiner concludes that, "Applicants' disclosure appears to be inconsistent with the results provided by these post-filing date references. Thus faced with contradictory and seemingly mutually exclusive results regarding the role of α_V or any intregin alpha subunit than can be cleaved by the MT-MMP on the angiogenic response . . . undue experimentation would be required . . . ." Office Action at page 4. However, the Examiner has not pointed out the "contradictory and mutually exclusive" results referred to, particularly in light of the actual text of these references.

Specifically, the Zhang article states "[i]n agreement with a VEGF-mediated angiogenic response, neovascularization was associated with αVB5, α1B1, and α2B1

integrins, as well as α5B1." Zhang at 955. Thus, there is no inconsistency between the present application and Zhang that α_V, α_1, α_2, and α_5 integrin subunits appear to be associated with angiogenesis in the corneal burn model of VEGF-mediated corneal angiogenesis.

Similarly, the alleged inconsistency between the Bergeron reference and the present specification actually supports the enablement of the presently claimed method. Bergeron is said to disclose that 9 of the 18 known subunits (α_3, α_4, α_5, α_6, α_8, α_9, α_{2b}, α_E and α_V) undergo post-translational cleavage at a site comprising pairs of basic amino acids. Applicants disclose that a set of α subunits including α_3, α_4, α_5, α_6, α_7,α_8, α_9, α_{2b}, α_E and α_V are capable of activation by MT1-MMP. See page 3-4 of the specification. Therefore, specific guidance is found in the present specification for choosing from among the known α subunits those that are susceptible of cleavage, and this guidance is supported (with the exception of α_7) by Bergeron, which was published after the filing date of this application.

Finally, the Examiner apparently alleges another inconsistency between Ratinov, which is said to disclose that MT1-MMP cleaves α_V, α_3 and α_5, but not α_2, and the present specification. However, as discussed in the last paragraph, the present specification does not indicate that α_2 subunit is so activated; indeed, the specification provides considerable guidance as to those integrin alpha subunits that can be activated by MT1-MMP, and lists among such subunits the α_V, α_3 and α_5 subunits. Thus, there is no inconstancy between the specification and this reference.

Enablement requires that the specification be sufficient to permit a person of ordinary skill in the art to make and use the claimed invention. The present specification sets forth various methodologies for the correlation of angiogenesis (in this case, corneal neovascularization) with MT-MMP1 activation of specific alpha subunits. Among these methods are anti-alpha subunit-specific antibody staining of developing vasculature (see, e.g., pages 12, 13, 28 and 29) and gelatin zymography, (pages 14 and 15). Antibodies to the known alpha subunits are commercially available, so the "making" of such antibodies or, by definition, identification of their specific antigens is a matter of routine. All that remains to be done is to incubate the cells, tissue, subunits or animal with the agent to be tested.

The Office Action appears to argue, because a single model system of angiogenesis was studied in the experiments disclosed in this specification (corneal angiogenesis, a VEGF-mediated angiogenic pathway which implicates α_VB5 and other integrin subunits), that Applicants disclosure is somehow inconsistent with the literature concerning other pathways, such as the bFGF-mediated angiogenesis pathway (which implicates α_VB3, among other integrin subunits). This not the case – Applicants have

claimed a generally useful method for the detection of angiogenesis associated with MT-MMP1 activation of alpha integrin subunits.

For the reasons stated above, Applicants believe the claims are free of this rejection, and therefore respectfully ask the Examiner to reconsider and withdraw this rejection.

35 USC §112(1) Written Description Rejection

Claims 11-17 also stand rejected over 35 USC 112(1) as allegedly lacking sufficient written description in the specification as filed. Applicants respectfully traverse this rejection.

Section 112 of Title 35 of the US Code requires that the specification contain a written description of the invention. The Court of Appeals for the Federal Circuit has recently rearticulated the basic rule that

> [t]he purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not; the applicant for a patent is therefore required to "recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." . . . [*Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991)]. Satisfaction of this requirement is measured by the understanding of the ordinarily skilled artisan. *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997) . . . .

Amgen, Inc. v. Hoescht Marion Roussel, Inc., 65 USPQ2d 1385, 1397 (Fed. Cir. 2003). (hereinafter *Amgen II*)

Claim 11, the sole pending independent claim, is drawn to:

> A method for determining whether an agent will inhibit an angiogenic response comprising
>
> a) contacting:
>
> i) an inactive pro form or convertase-activated form of an integrin α subunit involved in angiogenesis,
>
> ii) an agent to be tested for the ability to inhibit angiogenesis, and
>
> iii) metalloprotease MT1-MMP,

under conditions promoting an increase in activation of the integrin α subunit in the absence of said agent, and

correlating inhibition of said increase in integrin α subunit activation with the ability of the agent to inhibit angiogenesis.

As can be seen, this claim is drawn to a method rather than to a composition. As such, it is the steps of the method that must be the focus of any inquiry regarding patentability, rather than the structural attributes of a composition. The 2 steps of the claimed method are: 1) a contacting step and a 2) correlating step.

The three materials to be used in the contacting step are a) an agent to be tested for the ability to inhibit angiogenesis b) an inactive pro form or convertase-activated form of an integrin α subunit involved in angiogenesis, and c) metalloprotease MT1-MMP.

The question of adequate written description of claim 11, as articulated by the Court of Appeals for the Federal Circuit in the recent *Amgen II* case can thus be restated in the following way: would the "ordinarily skilled artisan" understand that the present inventors had conceived of the steps of the claimed method on or before the filing date of this patent application? Applicants respectfully contend that such an artisan would clearly attribute the present Applicants with conception of this claim at the time of filing the application.

Applicants submit that the present Office Action mistakes the appropriate law to be applied to the claimed methods. On page 5, it argues that "conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred . . . ." citing *Fiers v. Revel,* 25 USPQ2d 1601 (Fed. Cir. 1993) in support of this conclusion.

However the PTO's reliance on the doctrine of simultaneous conception and reduction to practice in the context of the present method claim is misplaced. The *Fiers* case addressed claims drawn to chemical compounds (nucleic acids), and noted, in conformity with *Amgen v. Chugai Pharmaceuticals, Ltd.* 18 USPQ2d 1016 (Fed. Cir. 1991) (hereinafter *Amgen I*) that a nucleic acid sequence cannot be conceived until it has been actually reduced to practice. The *Fiers* court held that, in such a case there cannot be adequate written description either, since the claimed novel compound is only capable of being described when its structure is known.

However, the present Applicants do not here claim that they have invented new compositions whose structure is heretofore unknown. Rather, the claims are drawn to

methods using materials (integrin α subunits and MT1-MMP) in conjunction with an agent (any chemical compound) whose effect on activated integrin alpha-mediated angiogenesis is to be determined. The National Center for Biotechnology Entrez database (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Protein) reveals 65 sequence entries when a search is done using the keyword "MT1-MMP" and 1760 entries when the keyword is "integrin alpha". Many of these entries, which are generally associated with scientific publications, predate the priority of this patent application.

Therefore, using the test set forth in *Amgen II*, the question is whether an "ordinarily skilled artisan", who must be deemed to have knowledge of the literature commensurate with this skill, would consider the description of the invention (including the originally filed claims) to adequately demonstrate that the claims were encompassed within the Applicant's original creation. Applicants submit that both the method steps of the claims, and the materials used in them, would be clearly understood by the person or ordinary skill in the art to have been invented by the present Applicants as of the priority date of the present application.

Reliance on the *Fiers* ruling, whose rationale arose from *Amgen I*'s "simultaneous conception and reduction to practice" doctrine, is neither appropriate nor applicable in the present case. If applied to method claims using known materials, the *Fiers* case would lead to the ridiculous result that every material used in a method, no matter whether known to a person of ordinary skill in the art or not, would need to described structurally in the specification in order for the method to be patentable. Terms such as "salt", "glycerol", "amino acid", and "beaker" would need literal structural basis in the specification. Of course, this is not the law.

The Office Action also cited the *PTO Final Guidelines on Written Description Requirement* (66 Fed. Reg. 1099 (Friday, January 5, 2001)) (the "Guidelines") in support of the rejection of these claims. In particular, the Office Action notes the Guidelines at 1106, third column. However, a review of this citation reveals that the indicated passage concerns claims drawn to claims to a genus of different species. Applicants do not claim a genus of different species, they claim a single general method; thus the cited passage is not applicant to the present invention.

Far from supporting a rejection of the pending claims, the Guidelines actually support their patentability. In the present case an original claim was presented for examination and rejected on written description grounds. The Guidelines indicate that in most cases "an originally filed claim is its own written description" (Guidelines, answer to comment 3, at 1100), and in all cases a strong presumption exists that an adequate written description of the invention originally claimed exists when the application is filed. *Id.* at 1105. Consistent with *Amgen II*, this strong presumption may be overcome by an

examiner who is able to demonstrate that an essential feature of the claimed invention is not known to one of ordinary skill in the art. *Id.*

However, the inverse is also true. The Guidelines clearly indicate that "information that is well known in the art need not be described in detail in the specification." *Id.* Where, as here, the materials are clearly known to the ordinarily skilled practitioner, the strong presumption is not overcome, and a prima facie case of unpatentability is not supported.

For the above-referenced reasons the Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection Pursuant to 35 USC §102(b)

Claims 11 and 14-17 were rejected as allegedly anticipated over Klotz et al., GRAEFES ARCH. CLIN. EXP. OPHTHALMOL. 238:88-93 (January 2000) "as evidenced by" Zhang et al., *supra*. Applicants traverse this rejection for the following reasons:

In order to anticipate, a single reference must disclose within its four corners each and every limitation of the challenged claim. See e.g., *Scripps Clinical & Research Foundation v. Genentech*, Inc. 18 USPQ2d 1001 (Fed. Cir. 1991). Moreover, an anticipatory reference must enable the claimed invention. *Id.*

Zhang et al. is not properly cited. First, the reference is not prior art to the present application. Secondly, even of Zhang were prior art, the allegedly anticipatory reference, Klotz, may not be combined with another reference in an attempt to make out a prima facie case of anticipation.

The Office Action attempts to use Zhang to "back fill" in an allegedly inherent claim element utterly missing from Klotz: the metaloprotease MT1-MMP. However, the Office Action indicates that Klotz teaches the screening of α_V subunit antagonists by assaying their effect on neovascularization. Even assuming for the same of argument that MT1-MMP is inherently present in the corneal tissue of Klotz (which Applicants do not admit), Applicants submit that the other major elements of the claimed method are also missing.

For example, claim 11 requires the presence of an inactive pro form or convertase-activated form of an integrin α subunit involved in angiogenesis, an agent to be tested for the ability to inhibit angiogenesis, and metalloprotease MT1-MMP,under

conditions promoting an increase in activation of the integrin α subunit in the absence of said agent, and correlating inhibition of said increase in integrin α subunit activation with the ability of the agent to inhibit angiogenesis.

Nowhere in Klotz does this correlating step appear; indeed, the Office Action does not address this portion of claim 11. Klotz directly measures the angiogenic response of corneal tissue to a test agent, and does not acknowledge the existence of MT1-MMP-cleaved species of the integrin alpha subunits at all.

By contrast, what is presently claimed is a screening method that can be used in the absence of, or in tandem with, a direct measurement of the angiogenic response. The focus of the claimed method is the activation or lack thereof of an integrin alpha subunit. As indicated in the specification, an inhibition of activation can be assayed by methods including detection of the appearance of a lower molecular weight integrin species due to MT1-MMP cleavage thereof, or of the reduction of the higher molecular weight non-activated alpha subunit.

Rejection pursuant to 35 USC §103(a)

Claims 11-13 were rejected as allegedly anticipated by Klotz et al., supra and Deryugina et al., cited as reference AB in the IDS filed in the present case. Again, the PTO cites a post-filing reference, Zhang et al, apparently as alleged evidence of inherency of the missing MT1-MMP element in Klotz, although this is not entirely clear in the Office Action.

The Office Action claims that the present invention differs from Klotz only in the "correlating" step, which is characterized as "observing a difference in migration of the activated form versus the inactive form in electrophoresis. However, this embodiment of the correlating step is present only in claim 12, and other claims such as claim 11 are not so limited by the method of correlating.

Perhaps more to the point, as mentioned above, Klotz et al., does not acknowledge the existence of MT1-MMP-cleaved species of the integrin alpha subunits at all, and does not mention observing the presence of such cleaved species as an indication of angiogenic activity, both material elements of all the present claims.

As correctly indicated by the Examiner, Deryugina discusses MT1-MMP "modification" of the B3 subunit including its higher electrophoretic activity, and examines the correlation of MT1-MMP expression with angiogenic activity. However, like the Klotz reference, Deryugina does not even mention or suggest the cleavage-

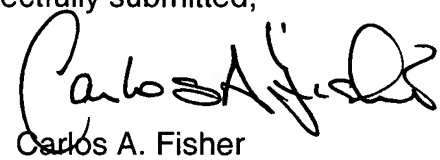
initiated activation of the integrin alpha subunits, focusing instead on protease cleavage of the integrin B3 subunit. If the combination of Klotz and Deryugina can be said to suggest anything at all, it would not be an examination of cleaved ingerin alpha, Iby cleaved integrin B3.

Since the present claim as a whole is not even suggested in the two references or their combination, Applicants respectfully request that the Examiner reconsider and withdrawn the present rejection.

CONCLUSION

Although no fee is thought to be due in connection with the present communication, if the Applicants are in error in this regard, the Commissioner is hereby authorized to use Despoit Account -1-0885 for the payment of any fee properly due.

Respectfully submitted,



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